

Appl. No. 10/004,800

Amdt. Dated Jun 26, 2003

Reply to Office action of Feb. 26, 2003

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1 to 41 are in the case.

Claim Objections

The Examiner objected to claim 37 for failing to provide an antecedent basis for "precursor ions". In response, claim 36 from which claim 37 depends has been amended, and new claim 41 has been added. Specifically, as amended, new claim 36 depends from claim 34, which provides an antecedent basis for "precursor ions" and no longer depends from claim 33, which does not provide an antecedent basis for "precursor ions". The language of new claim 41 parallels that of claim 36 except that new claim 41 depends from claim 33 and not from claim 34.

Claim Rejections – 35 USC, s. 103

The Examiner has rejected claims 1-4 and 31 as allegedly unpatentable over Clemmer (U.S. patent No. 6,326,482), in view of Franzen (U.S. patent No. 5,572,035), and has rejected claims 5, 6, 8-19, 21, 23-25, 29, 30 and 32-35 as being unpatentable over Clemmer in view of Franzen as applied to claim 1 and in further view of Thomson (U.S. patent No. 6,111,250) and in still further view of Smith (U.S. patent No. 6,107,628). These rejections are respectfully traversed, and it is respectfully submitted that the present invention as claimed is patentable over the combined teachings of Clemmer, Franzen, Thomson and Smith. Before addressing this argument in detail, the invention and its relationship to the known art is summarized below.

Background and Summary of the Invention

The present invention relates to a hybrid mobility-mass spectrometry apparatus, and a new method of using such a hybrid device. The hybrid mobility-mass spectrometry apparatus involves both mass spectrometry and ion mobility spectrometry.

Presently, there are a wide variety of different analysis techniques known for analyzing solvents and substances of interest. Two such analysis techniques are mass spectrometry and ion mobility spectrometry.

Fundamentally, all mass spectrometry mass analysis instruments operate at low pressures. Separation of different ions by the mass spectrometer depends solely upon different mass-to-charge ratios of the ions present. A problem arises when there are two similar ions that have identical or similar mass-to-charge ratios. Such ions are considered to be isobaric, and cannot be separated by conventional mass spectrometry techniques.

In ion mobility spectrometry (IMS), a substance to be analyzed is ionized, to the extent possible, as is required in the low pressure mass spectrometry described above. However, as IMS is currently carried out at higher pressures, even at atmospheric

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pressure, the techniques for ionization are necessarily different than those used for mass spectrometry. Preferably, a known, selected gas that is dry, clean and pure and has known properties is provided to the drift tube. Ions are then caused to travel down the drift tube under a potential gradient, through the gas. Different ions have different mobility characteristics depending upon the size and type of the ion and its charge. Thus, different ions will have different transit times to traverse the drift tube. Ions are detected at a detector at an exit from the drift tube, and, knowing transit times for different ions, the constituent components of a sample can be determined.

As described above, there are some ions that mass spectrometry will be unable to easily distinguish. Similarly, there are other ions that ion mobility spectrometry will be unable to easily distinguish. In this and other analogous situations, it is advantageous to provide two-dimensional separation, which involves two different steps. That is, a first set of ions may be difficult to separate using a first separation process, while a second set of ions may be difficult to separate using a second separation process. However, the first set of ions is likely to be somewhat different than the second set of ions. Thus, using a two-dimensional process, one could separate all ions except those ions that are both in the first set of ions and the second set of ions – i.e. those ions that cannot be separated using either the first separation process or the second separation process. By combining IMS with mass spectrometry, two separate steps are provided. Thus, the second separation step may succeed in separating ions that could not be distinguished by the first separation step.

There is, however, a second advantage to combining IMS and mass spectrometry that is peculiar to these two processes. That is, one of the disadvantages of time-of-flight mass spectrometers is that they inherently require pulsed intermittent operation. Once a pulse of ions has been injected to the flight tube of the mass spectrometer, it is necessary to wait until all of the ions in the sample have traveled the length of the flight tube and been detected before injecting the next pulse. Otherwise, late arriving ions from a previous pulse may contaminate a reading taken for a subsequent pulse. The need to wait until all of the ions have cleared the flight tube results in a poor duty cycle, particularly where the sample of ions has a wide m/z ratio.

One of the advantages of combining IMS with mass spectrometry is that there is an approximate correspondence between ion behavior and the two separation steps. Thus, in both IMS and low pressure mass spectrometry, a heavy ion will take longer to traverse the instrument due to a large m/z ratio. That is, a heavy ion will take longer to pass through a low pressure mass spectrometer, and will also have a low mobility resulting in a large drift or transit time through an IMS device. As a result, lighter ions will pass through the IMS device more quickly, while heavier ions take a longer time. This provides grouped input to the mass spectrometer, in which the faster ions are provided first and the m/z ratio range for each pulse or group is reduced as the IMS device has already separately grouped, to some extent, ions having widely different m/z ratios.

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To some extent, ion output from the IMS must be modified before being accepted by the downstream low pressure mass spectrometer. That is, the diameter of the ion beam exiting the IMS section is much larger than the acceptance of the low pressure mass spectrometer as radial spread of the ion beam is inherent in the nature of IMS. Without modification, the resolution or sensitivity of a high performance, low pressure mass spectrometer would be compromised.

Claims 1, 29, 31, 32 and 33 have been amended to more clearly define the invention. That is, claim 1 has been amended to better define the location of the RF ion guide. Claim 29 has been amended to explicitly recite an RF ion guide to focus the ions along its axis. Corresponding amendments have been made to claim 31, which depends from claim 29. New claim 43 depending from claim 29 has been added covering the case in which the collision cell comprises the RF ion guide.

Similarly, claim 33 has been amended to explicitly recite passing the ions through an RF ion guide to focus the ions along its axis. New claim 42 depending from claim 33 has been added covering the case in which the ions are concurrently passed through the RF ion guide and the collision cell.

Detailed Reply to Claim Rejections

Clemmer discloses a hybrid mobility-mass spectrometry apparatus involving both IMS and mass spectrometry. As described above, the diameter of the ion beam exiting the cell taught by Clemmer is much larger than the acceptance of the orthogonal time-of-flight analyzer. Clemmer attempts to narrow the ion beam by focusing the beam using ion optics in the form of a DC lens (Figure 4, reference No. 47). However, this narrowing of the ion beam will still not be to an acceptance level equivalent to the time-of-flight mass spectrometer. Although not specifically disclosed by Clemmer, at best a resolution on the order of 1000-2000 FWHM can be achieved using such a hybrid system. Commercially, this is unacceptable since high performance time-of-flight mass spectrometers can easily achieve five times that resolution.

The Examiner takes the position that the present invention would be obvious in view of the combined teachings of Clemmer and Franzen, as the RF ion guide taught by Franzen could be used to replace the DC lens used in Clemmer. This position is respectfully traversed. Specifically, there is an understanding in the art that to use an RF ion guide as a focusing device will limit the resolution of the mobility spectrometer, as the RF ion guide will tend to "stretch" out the ion beam, thereby counteracting the tendency of the IMS device to provide a pulsed ion output.

This understanding in the art is illustrated in United States patent No. 6,331,702, as well as in two papers: A. N. Kruthinsky, I.V. Chernushevich, V.L. Spicer, W. Ens, and K. G. Standing, "Collisional Damping Interface for an Electrospray Ionization Time-of-Flight Mass Spectrometer", *Journal for the American Society of Mass Spectrometry*, 1998, Vol. 9, 569 to 579, published online by Elsevier Science; and, A. N. Kruthinsky, A.V. Loboda, V.L. Spicer, R. Dworschak, W. Ens, and K. G. Standing, "Orthogonal Injection

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of Matrix-assisted Laser Desorption/Ionization ions into a Time-of-flight Spectrometer Through a Collisional Damping Interface", *Rapid Communications in Mass Spectrometry*, 1998, Vol. 12, 508 to 518, published online by John Wiley & Sons. For example, column 7, line 21 to line 28 of United States patent No. 6,331,702 reads as follows:

The RF quadrupoles 31 and 32 with a damping gas between their rods can be run in an RF-only mode, in which case they serve to reduce the axial energy, the radial energy, and the energy spreads, of the ions which pass through it, as will be described. This process substantially spreads the plume of ions out along the ion path, changing the initial beam, pulsed at about 13 Hz, into a quasi-continuous beam as described in more detail below.

Please also see column 8 of this patent at line 5 to line 13:

The radial energy distribution, while much smaller than the axial energy is still sufficient to cause substantial spreading and expansion of the beam as it leaves the quadrupole rod set 32 and travels towards the TOF axis. The spatial spread of the beam along the TOF axis limits the resolution.

The Collisional Damping paper describes an electrospray ionization (ESI) source, which is usually a continuous beam ion source, but has been adapted to pulse ions through an RF ion guide into a Time-of-flight mass spectrometer. Krutchinsky et al. investigate what happens to spatial integrity when these ions are pulsed into the ion guide. First, the authors describe a theoretical model that indicates that there is significant ion velocity damping when ions are transported through the ion guide. Specifically, on page 572, the authors describe damping by at least a factor of 6 for the radial velocity and by a factor of 14 for the axial velocity. These results are illustrated in Figs. 4a-d.

Secondly, the authors experimentally measure the time delay of ions passing through the RF ion guide. As reported on page 573, ions were pulsed every 300 microseconds into the ion guide. As indicated in Fig. 6, these ions emerged from the exit of the ion guide spread over a width of 1.3 to 1.6 ms. That is, if ions are spatially separated by 300 microseconds upstream of the ion guide, they will tend to overlap leaving the ion guide. Any initial resolved mass distribution upstream of the ion guide will thus be lost downstream of the ion guide (as in the case where an ion mobility device was used to do the initial mass separation upstream from the RF ion guide).

The Orthogonal Injection paper describes using a MALDI ion source (a pulsed ion source) to inject ions through an RF ion guide to create a continuous beam of ions. The authors teach that by using the RF ion guide, the discrete pulses of ions are converted into a quasi-continuous beam as the collisional damping caused by the RF ion guide

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causes spreading of the ion beam out along the quadrupole axis (see pag 513, last paragraph).

Thus, based on the foregoing references it is respectfully submitted that the use of an RF ion guide to focus an ion beam received from a mobility spectrometer would not have occurred to those skilled in the art as they would have concluded that the RF ion guide would counteract the tendency of the IMS to provide a pulsed ion output. There is nothing in the teachings of either Clemmer or Franzen to suggest replacing the DC lens taught by Clemmer with the RF ion guide taught by Franzen. Further, the shared understandings of those skilled in the art would militate against this combination. That this is the case can be inferred from the fact that neither Clemmer nor Franzen nor Thomson nor Smith teach the use of an RF ion guide for the purpose of focusing and maintaining the temporal spacing of ions between an ion mobility section and a mass analyzer section in a hybrid mobility-mass spectrometry apparatus despite the known problems with the Clemmer device resulting from its reliance on the DC lens.

Based on the foregoing, it is respectfully submitted that amended claim 1 is unobvious over the teachings of the patents cited. That is, claim 1 recites an ion focusing section for receiving ions from the ion mobility section that includes an RF ion guide that generates a field to promote focusing of the ions in the radial dimension along the axis of the RF ion guide. The use of an RF ion guide for this purpose is not taught in the prior art, nor is it consistent with the teachings of the prior art, which teachings indicate that an RF ion guide is unsuitable for this purpose as it will tend to spread out the pulses emitted by the IMS.

Claim 16 covers a method of separating ions based on ion mobility characteristics in which an RF ion guide is included downstream from a drift region and upstream from a mass analyzer. The RF ion guide receives ions from the drift region, and focuses the ions along an axis of the RF ion guide such that the ions can then be passed into the mass analyzer. Similar to the case with claim 1, the patents cited do not teach the use of an RF ion guide for this purpose; indeed, this use of an RF ion guide is inconsistent with the teachings of the prior art.

It is respectfully submitted that amended claims 29 and 33 are unobvious over the teachings of the patents cited. That is, both of these claims recite using an RF ion guide that generates a field to promote focusing of the ions in the radial dimension along the axis of the RF ion guide. The use of an RF ion guide for this purpose is not taught in the prior art, nor is it consistent with the teachings of the prior art, which teachings indicate that an RF ion guide is unsuitable for this purpose as it will tend to spread out the pulses emitted by the IMS.

In view of the foregoing, it is respectfully submitted that the claims are allowable over the cited references. Allowance of the application is respectfully requested.

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If any questions arise, it is requested that the undersigned be contacted at the number provided below.

A request for a one-month extension of time for response is being filed concurrently herewith under separate cover, titled *Petition for Extension of Time Under 37 CFR 1.136(a)*. Please charge the government fee of \$110.00 to our firm's Visa account. Please also charge any deficiencies or credit any overpayments to this account.

Respectfully submitted,

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